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PATENT APPLICATION

OFFICIAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

James **CASTILLO**

Application No.: **09/954,494** Examiner: **Kim, Vickie**

Filed: **September 17, 2001** Group Art Unit: **1614**

For: **ALCOHOL BASED TOPICAL ANESTHETIC FORMULATION AND METHOD**

Attorney Docket: **3863.015**

Customer number: **000041288**

DECLARATION UNDER 37 C.F.R. §1.130

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, James Castillo, 15412 15th Street, Lutz, Florida 33549, declare and state the following:

In March of 1980, I graduated from the University of Florida with a Bachelors Degree in Pharmacy.

I have been involved in research and development relating to pharmacology, and particularly anesthetics, since 1986, and consider myself an expert in this field.

I am familiar with the subject matter and prosecution history of the above-identified application, including the Office Action dated December 22, 2003.

I note the Examiner's obviousness type rejection under 35 U.S.C. 103(a) of Claim 16 of the above-identified application in view of US Patent No. 6,485,714 to Mangione et al.

U.S. Patent Application No. 09/954,494
DECLARATION UNDER 37 C.F.R. §1.130

Attorney Docket: 3863.015

I respectfully request the Examiner to withdraw this rejection in view of the following factor:

1) the '714 patent was issued on November 26, 2002, which is more than one year prior to the filing date of the present application, September 17, 2001.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application and of any patent issuing thereon.

Date: 5-12-04

James Castillo

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I am familiar with the subject matter and prosecution history of the above-identified application, including the Office Action dated December 22, 2003.

I note the Examiner's position in the Final Office Action dated December 22, 2003, i.e., that the Declaration filed July 9, 2003, is insufficient to overcome the rejection of the pending set of claims in view of the anticipation rejection by Inagi et al. (US Patent 6,429,228). According to the Examiner, the comparative example was done by choosing a composition of the Inagi reference which uses less amounts of alcohol (33%) than the amount of alcohol of the present

invention (42-44%). In addition, the Examiner is of the opinion that the presence of oleic acid will change the evaporation rate if included in the Inagi composition. Furthermore, the Examiner indicated that Compositions 11 and 16 of the Inagi reference contain a higher content of alcohol than composition 1 used for the comparative example.

Finally, the Examiner is of the opinion that compositions 2 and 10 of the Inagi reference are closer to the composition of the present invention than the composition used during the comparative example.

I have conducted the following comparative experimentation to demonstrate that:

1) the limitations evaporation cannot be considered an inherent feature of the composition disclosed by Inagi et al; and

2) the composition according to the present invention has a better onset than the compositions of Inagi.

Point 1

In order to prove to the Examiner that the composition of the Inagi reference has a very low evaporation rate (if any), we performed an evaporation test on the specific compositions cited by the Examiner, namely compositions 2, 10, 11, and 16 of the Inagi reference and the composition according to the present invention.

That is, in order to demonstrate the unexpected improvement in evaporation, the following experimentation was conducted by me, or under my direct supervision.

Results of the evaporation test are shown on Table 1.

PROCEDURE

BETACAINE GEL (Present invention)

Ingredient Amount

Carbopol 940 SPECTRUM	1.05 gm
Water, distilled	29.42 ml
Polysorbate 80	1.05 ml
Lidocaine	5.0 gm
Petrolatum, white	12.45 gm
Alcohol, Isopropyl	51.03 ml

DISSOLVE CARBOPOL IN HOT WATER(45 C-50 C). MIX WELL TO DISPERSE ALL THE CARBOPOL.

THERE SHOULD BE NO VISIBLE LUMPS OF CARPOBOL. ADD PS 80 IN SMALL AMOUNTS WHILE MIXING VIGOROUSLY.

HEAT PETROLATUM TO 45 C. DISSOLVE LIDOCAINE IN PETROLATUM. ADD THIS MIXTURE TO THE CARBOPOL,

PS 80, AND WATER MIXTURE. MIX WELL. SLOWLY ADD THE ALCOHOL TO THIS MIXTURE WHILE VIGOROUSLY MIXING.

INAGI ET AL. FORMULA NUMBER 2

Ingredient	Amount (% weight)
Lidocaine	10.0
Oleic acid	0.8
Isopropyl alcohol	30.0
Sodium caprylate	2.4
Polyvinyl alcohol	10.0
Purified Water	46.6
Hydrochloric acid	0.2

The weight ratio alcohol/water is 0.64

INAGI ET AL. FORMULA NUMBER 10

Ingredient	Amount (% weight)
Lidocaine	10.0

Oleic acid	0.5
Isopropyl alcohol	28.0
Sodium caprylate	3.0
Polyvinyl alcohol	10.0
Purified Water	47.5
Lactic Acid	1.0

The weight ratio alcohol/water is 0.59

INAGI ET AL. FORMULA NUMBER 11

Ingredient	Amount (% weight)
Lidocaine	10.0
Ethanol	42.0
Sodium caprylate	2.0
Polyvinyl alcohol	10.0
Purified Water	35.8
Hydrochloric acid	0.2

The weight ratio alcohol/water is 1.17

INAGI ET AL. FORMULA NUMBER 16

Ingredient	Amount (% weight)
Lidocaine	10.0
Oleic acid	3.0
Isopropyl alcohol	44.0
Polyvinyl alcohol	10.0
Purified Water	32.9
Hydrochloric acid	0.1

The weight ratio alcohol/water is 1.34

The compositions were prepared following the instructions in column 6, lines 10-25.

Approximately five grams of each formulation were placed on glassine paper and then spread out so that each sample had the same surface area. The results are as follows:

TABLE 1

Time (min)	Weight (gm) Inagi 2	Inagi 10	Inagi 11	Inagi 16	Alcohol Gel
0	5.55	5.55	5.55	5.55	5.55
5	5.45	5.47	5.46	5.46	4.45
10	5.30	5.28	5.34	5.33	3.43
15	5.24	5.12	5.26	5.26	2.94
20	5.11	5.02	5.14	5.12	2.50
25	4.98	5.00	5.02	4.98	2.17
30	4.96	4.97	4.95	4.94	1.98

PART 2

In order to demonstrate the composition according to the present invention has a better onset than the compositions of Inagi, the following experimentation was conducted by me, or under my direct supervision.

A Double-Blind Study of Topical Betacaine® Enhanced Gel 10 (10% lidocaine) versus Selected Inagi formulas in the Prevention of Topically Induced Pain

STUDY SYNOPSIS

This is a double-blind, prospective evaluation of topical anesthetics (Betacaine Enhanced Gel 10 and versus Selected Inagi formulas) in the prevention of topically-induced pain.

Twenty subjects, 18 years of age or older, were enrolled. The subjects were divided into four groups of five. Each group was assigned one of the Inagi formulas to test against Betacaine Enhanced Gel.

Test sites were the inner aspect of the forearms. The arms were

cleansed, and the medications applied to the areas to be tested. A small, but equal amount, of each medication were applied by the investigator to an area from the antecubital fossa to mid-point of each forearm and left in place for 25 minutes without occlusion.

At the mid-aspect of the forearm within the area of anesthesia, subjects' skin was pricked with a standard sterile 27-gauge needle and asked to evaluate the degree of sensation using a 1-5 scale. Another needle prick was performed in an area near the wrist (below the area of application) to determine the degree of pain using the same 1-5 scale as previous. This was performed on both arms distal to the area of anesthesia.

DESCRIPTION OF THE TOPICAL ANESTHETICS

Betacaine Enhanced Gel (Castillo) was prepared according to point 1.

Inagi formulas:

Component	Example (% by weight)			
Composition No.	2	10	11	16
Lidocaine	10	10	10	10
Oleic acid	0.8	.5	-	3
Ethanol	-	-	42	44
Isopropyl Alcohol	30	28	-	-
Sodium Caprylate	2.4	3	2	-
Polyvinyl Alcohol	10	10	10	10
Purified Water	48.6	47.5	35.8	32.9
Hydrochloric	0.2	-	0.2	0.1

Acid				
Lactic Acid	-	1	-	-

OBJECTIVES

The objectives of this study are the following:

- Evaluate the degree of anesthesia provided by Betacaine Enhanced Gel 10 compared with the degree of anesthesia provided by selected Inagi formulas with control being no agent applied to provide anesthesia
- Document any adverse events that may occur

STUDY POPULATION

Participants in the study were male or female, 18 years of age or older. All subjects at the clinical sites who fulfill the inclusion/exclusion criteria and who elect to participate in the study were included in the evaluation.

5.1 Inclusion Criteria

- Subject must be 18 years of age or older
- Subject must be able to understand and sign the informed consent.
- Subject must be willing to participate in the study

5.2 Exclusion Criteria

- Subject must not be allergic to any topical anesthetics
- Subject must not have a personal history of atopic, allergic or anaphylactic reactions
- Subject must not have any active skin disease in the areas to be tested
- Subject must not have had a rash or applied topical medication to the areas to be tested in the prior 2 weeks
- Subject must not be pregnant or breast-feeding
- Subject must not currently be receiving prednisone, other

immunosuppressive medication, anti-histamines or pain medications

- Subject must not have enrolled in any other clinical trial within the last 6 months
- Subject must not have a neurologic deficit in the area to be tested. Subject must not have a chronic neurologic disease, which may affect pain perception

STUDY DESIGN

This was a randomized, double-blinded, prospective evaluation. They were treated in a random fashion on either the left or the right arm with the 2 products.

Qualification and Enrollment of Subjects

All subjects 18 years of age and older who volunteer were considered for enrollment in this trial. Prior to initiation of the study, subjects were qualified for participation in the trial, according to the inclusion and exclusion criteria. Subjects who meet all of the eligibility criteria were invited to participate. Study personnel explained the study to the subject, including the purpose, benefits, risks and human subject rights. The subject was given the consent form and allowed as much time as required to read and decide on participation. If the subject chooses to participate, he or she was enrolled.

Treatment Site

Before the subject was enrolled, it was explained that the test site for this study consists of both forearms.

Treatment Procedure

After cleansing the medial aspect of both forearms with a mild cleanser such as Cetaphil®, the area was prepped with alcohol and cotton and dried. Sufficient quantity of each test product randomly chosen as to left and right was applied to the area cleansed, leaving a thin film of each product on the skin equally on both arms.

The medications remained in place 25 minutes and then any visible residual product was removed with dry gauze.

Evaluation by the patient occurred immediately according to the scale provided (See section 8.0).

The subject's arms were pricked with a 27g sterile needle at the mid-point of each forearm and in one area at the wrist and evaluated in these 3 sites by the patient on the scale provided.

Cleanse the areas of the needle pricks with alcohol.

MATERIALS AND SUPPLIES

The following materials and supplies were provided by the study sponsor:

- Betacaine® Enhanced Gel 10 with label covered and with code number
- Four Inagi formulas (2, 10, 11, and 16) with code number
- Code number identification to be supplied to Study Coordinator
- Informed Consent Forms
- Clinical Report Forms
- Adverse Event Forms
- Protocol

STATISTICAL CONSIDERATIONS

Sample Size

Since each subject was tested with both products and additionally tested in an area where no medication was applied, each subject serves as a control. 20 subject should, therefore, be sufficient to allow evaluation.

Randomization

Each subject had the 2 topicals randomized as to which is applied to which arm and which is applied first.

Endpoints

Blinded evaluation by the subject with regard to the pain associated with a needle prick by a 27 g needle.

The subject evaluated the sensation in each forearm and in an area near the wrist using the same scale as above.

The results of the test are shown on Table 2.

Table 2
Needle Prick Results

Composition	Inagi 2	Inagi 10	Inagi 11	Inagi 16	Castillo
Arm	3.8	3.6	3.4	3.4	2.2
Wrist	4.2				

CONCLUSION

As can be seen from the results of the test, the formulation of the present invention shows a remarkable evaporation rate over the compositions of the Inagi et al. reference.

The composition of the present invention does not use water, thus the evaporation rate of the volatile solvent is higher than the evaporation rate of a composition that utilizes water. This remarkable evaporation rate allows the kinetic of the formulation to change so that as the proportion of the remaining alcohol is reduced, a more concentrated anesthetic formulation remains present on the skin, which brings a more advanced level of anesthetization. Thus, the delivery rate of the anesthetic is markedly enhanced.

In addition, because the onset of the anesthetic is reduced, the waiting time from the patient is also reduced; thus, the patient has a more tolerant attitude.

As a side benefit, the evaporation of the alcohol cools the skin causing the patient to feel a soothing cool, numbing feeling, which psychologically prepares the patient to the effect of the anesthetic.

In the Inagi et al. reference, the acceptable delivery rate of the medicament that needs to be delivered through the skin is lowered because the low evaporation rate of the composition, thus the anesthetic will take a longer time to act. Furthermore, because of the low evaporation rate, it is possible that alcohol can interact with the patient's skin and cause irritation. As can be seen, the Inagi et al reference does not overcome the problem of the prior art.

In addition, because the onset of the anesthetic is reduced, the waiting time from the patient is also reduced, thus the patient has a more tolerant attitude.

As a side benefit, the evaporation of the alcohol cools the skin causing the patient to feel a soothing cool, numbing feeling, which psychologically prepares the patient to the effect of the anesthetic.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application of any patent issuing thereon.

In the Inagi et al. reference, the acceptable delivery rate of the medicament that needs to be delivered through the skin is lowered because the low evaporation rate of the composition; thus, the anesthetic will take at least 30 minutes (longer time to act.) (column 7, lines 29-34)

This delay in onset is a significant disadvantage, as it is a great inconvenience for both patients and medical staff. Such delay is particularly a problem in the area of pediatrics, where any additional time spent awaiting treatment only contributes to the anxiety of the patient.

As a side benefit, the evaporation of the alcohol cools the skin, causing the patient to feel a soothing cool, numbing feeling, which psychologically prepares the patient to the effect of the anesthetic.

In addition, the prolonged contact of the alcohol with the skin can cause skin irritation. As can be seen, the Inagi et al reference does not overcome the problem of the prior art.

Furthermore, after much of the alcohol has evaporated, the kinetics of the formulation change so that, as the proportion of remaining alcohol is reduced, a more concentrated anesthetic formulation remains present on the skin, which brings about a more advanced level of anesthetization.

Thus, by using the formulation of the present invention, the delivery rate of the anesthetic is markedly enhanced, the method of administration remains simple, the incidence of side effects

associated with many penetration enhancers is reduced or eliminated, topical irritation is avoided, and the comfort level of the patient is increased as the patient has the perception that the formulation is taking effect.

Date: 5-12-04

James Castillo